--75. The method of claim 47 wherein said administration prolongs survival of said patient.

--76. A method of treating a malignant tumor in a human patient comprising administering to the patient a composition comprising a therapeutically effective amount of human tumor cells that:

(i) are conjugated to a hapten;

(ii) are of the same tumor type as a malignant tumor of a patient for treatment of whom the composition is intended;

(iii) are autologous to said patient; and

(iv) have been rendered incapable of growing in the body of a human upon injection therein;

wherein said administration elicits T lymphocytes that infiltrate the tumor of said human, said lymphocytes being predominantly $CD8^{+}CD4^{-}$.--

REMARKS

Reconsideration of this application is respectfully requested.

Upon entry of this Amendment under 37 C.F.R. §1.129, the Amendment filed May 4, 1998 will also be entered. Thus, claim amendments made herein are to the claims as amended by the May 4, 1998 Amendment.

By the present amendment, claims 2, 3, 5-7, 10, 22, 24-28, 34-42, 45, 46, and 48

have been canceled. New claims 49-76 have been added to more fully claim that which Applicant regards as his invention. Claims 49-69 and 71-75 correspond to previously pending dependent claims except that they now depend from claims 43, 44 or 47. Claim 70 finds support in the specification page 18, lines 16 to 17. Claim 76 finds support in the specification page 23, lines 5 to 7. No new matter has been added.

In the Advisory Action mailed September 11, 1998, the Examiner has indicated that the Amendment filed May 4, 1998, if entered, would overcome all rejections under 35 U.S.C. 112, 1st and 2nd paragraphs. However, the Examiner has stated that prior art rejections would be reinstated. Accordingly, a response to these prior art rejections is included herewith.

Obviousness-type Double Patenting Rejection

Claims 2, 3, 5-7, 10, 22, 24-28, 34-42 and 45-48 stand rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Patent No. 5,290,551 to Berd.

Claims 2, 3, 5-7, 10, 22, 24-28, 34-42, 45 and 48 have been canceled. The rejection with respect to these claims is now moot.

With respect to claim 47, Applicant respectfully traverses this rejection. Claim 47 and new claim 76 call for a method of treating cancer by administering human tumor cells by repeating administration for at least 6 times (claim 47) or wherein said administration elicits predominantly $CD4^{-}CD8^{+}$ T lymphocytes (claim 76). These claims are not suggested by the claims of the '551 patent. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §102(a)

Claims 2, 3, 5-7, 10, 22, 24-28, 34-42, 45, 46 and 48 stand rejected under 35 U.S.C. §102(a) over Murphy *et al.*, *Lab. Investigation*, 1990 62(1)70A. These claims have been canceled. New claims 49 to 75 depend from claims 43, 44 and 47 and are thus not anticipated by Murphy *et al.*

New claim 76 calls for a method of treating cancer by administering hapten-conjugated human tumor cells wherein said administering elicits predominantly $CD4^-CD8^+$ T lymphocytes. The $CD4^-CD8^+$ limitation is not disclosed by Murphy *et al.* Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §102(b)

Claims 2, 3, 5-7, 10, 22, 24-28, 34-42, 45, 46 and 48 stand rejected under 35 U.S.C. §102 over Berd *et al.*, *Proc. Am. Assoc. Cancer Res.*, 1989, 30, 382. These claims have been canceled and the rejection is now moot. Withdrawal of the rejection is respectfully requested.

New claim 76 calls for a method of treating cancer by administering hapten-conjugated human tumor cells wherein said administering elicits predominantly $CD4^-CD8^+$ T lymphocytes. The $CD4^-CD8^+$ limitation is not disclosed by Berd *et al.* Accordingly, claim 76 is independently patentable.

Rejection under 35 U.S.C. §103

The claims in this application have been rejected under 35 U.S.C. §103 on the following two grounds:

I. Claims 2, 3, 5-7, 10, 22, 24-28, 34-42, 45, 46 and 48 stand rejected as obvious over Berd *et al.*, *Cancer Res.*, 1986, 46:2572-77 in view of Fujiwara *et al.*, *J. Immunol.*, 1980, 124:863, Fujiwara *et al.*, *J. Immunol,* 1984, 133:510-14, and Getzy *et al.*, *J. Immunol.*, 1970, 19:189-203. These claims have been canceled and the rejection is now moot. Withdrawal of the rejection is respectfully requested.

II. Claims 43, 44 and 47 stand rejected as obvious over McCune *et al.*, *Cancer*, 1981, 47:1984-87 or McCune *et al.*, *Cancer*, 1979, 43:1619-23 in view of Berd *et al.*, *Cancer Res.*, 1986, 46:2572-77, Fujiwara *et al.*, *J. Immunol.*, 1980, 124:863, Fujiwara *et al.*, *J. Immunol,* 1984, 133:510-14, and Getzy *et al.* , *J. Immunol.*, 1970, 19:189-203. This rejection is respectfully traversed.

Both McCune references disclose treating metastatic renal carcinoma by administering autologous, irradiated tumor cells mixed with an adjuvant. The McCune tumor cells were *not* conjugated to a hapten and thus the composition administered by McCune is *different* from the composition that is administered according to the present invention. These two compositions (*i.e.*, tumor cells with or without hapten) have distinct results as shown in the present specification. The results described in the Example 4 of the specification (page 30, lines 23-27) show statistically significant differences between the effectiveness of a tumor cell vaccine

of the prior art (*i.e.*, human tumor cells without hapten) and the vaccine of the invention (*i.e.*, human tumor cells conjugated to a hapten). The ability of the vaccine comprising hapten-modified melanoma cells to prolong disease-free survival and total survival in treated patients, for example, is significantly higher ($p < 0.01$) than the same ability of the vaccine comprising non-conjugated tumor cells. Example 6 of the present specification shows that hapten-modified tumor cells can increase total survival rate from 27% to 59% (page 42, lines 1-5). Thus, the vaccine of the invention is more effective than the McCune vaccine. The McCune references neither disclose nor suggest that using hapten-conjugated tumor cells would result in these unexpected advantages. Without such a suggestion, one skilled in the art would not have had a reasonable expectation of success that a vaccine described and claimed herein can be produced by modifying the vaccine of McCune by conjugating hapten to tumor cells.

Additionally, the vaccine composition of the present invention functions by inducing a cellular (T cell) response. The composition elicits T lymphocytes that infiltrate the tumor of the patient and cause inflammation of the tumor. There is no teaching or suggestion in the McCune references that such a result would occur by administering hapten-conjugated tumor cells. For these reasons, a person of skill in the art would not have reasonably expected as of the filing date of this application (based upon the teaching of the McCune references) that conjugating hapten to tumor cells would cause infiltration by lymphocytes and tumor inflammation. Hence, for the finding of obviousness to be proper, other cited references (*i.e.* , Berd 1986, Fujiwara 1980 and 1984 and Getzy) must provide (i) a motivation to conjugate a hapten to the autologous, irradiated tumor cells of McCune and (ii) a reasonable expectation of

success that the resulting vaccine would elicit T lymphocytes that infiltrate the tumor, cause tumor inflammation and would be effective. No such motivation or suggestion of success can be found in any of the cited references alone on the combination as shown below.

The Berd 1986 reference teaches a melanoma tumor cell vaccine in which tumor cells are *not* conjugated to a hapten. Hence, the reference is cumulative with McCune references and adds no suggestion or expectation of success that administering hapten-conjugated tumor cells would be effective or that the composition thereof would have any of the properties recited in the present claims.

The Fujiwara 1980 describes an experimental system in mice based on immunoprophylaxis which is different from the immunotherapy described in the present specification. Fujiwara 1980 discloses a composition containing haptenized mouse tumor cells and differ from the present invention in the following respects:

Fujiwara 1980 describes application of TNP-modified mouse LSTRA cells for immunoprophylaxis. In other words, a normal mouse is immunized with a hapten TNP. Several weeks later, the spleen cells from the TNP- immunized mouse are mixed with live tumor (LSTRA) cells and injected into normal mice (see Fujiwara 1980, page 865, last ¶). The growth of this induced tumor is then measured and compared to the growth of the tumor induced by injecting viable LSTRA cells mixed with spleen cells from mice immunized with LSTRA cells only (*i.e.*, not conjugated to TNP). Thus, the ability of TNP-LSTRA cells to prevent the growth of a newly induced tumor is measured.

In contrast, the *hapten*-conjugated human tumor cell composition of the present

invention is used in immunotherapy, in which a patient has a growing spontaneous tumor and the composition is effective at treating the tumor by causing its infiltration by T cells and inflammation. There is no teaching or suggestion in the Fujiwara 1980 reference that TNP-modified tumor cells that could slow down the growth of a new, induced tumor would have any effect in a human patient in need of treatment. At best, the reference is an invitation to experiment and provides no expectation of success even when combined with the McCune and Berd 1986 references.

Fujiwara 1980 describes transplantable mouse tumor cells conjugated to TNP, which tumor cells originate from a tumor induced by a carcinogenic agent in one mouse and where extracts of that tumor are then injected into other mice to induce a tumor. In contrast, the composition of the present invention is derived from human tumors which are spontaneous. It is well known in the art that induced tumors are easier to manipulate than spontaneous tumors. First, induced tumors are easier to treat because they tend to be immunogenic, and second, results obtained with induced tumors are difficult to apply to treatments for spontaneous tumors. For example, Hewitt *et al., Br. J. Cancer,* 1976, 33:241-259 describe the differences between spontaneous and induced tumors. Hewitt teaches that "practically all the animal data presented in support of a general theory of tumor immunogenicity or to provide a basis for active clinical immunotherapy have been obtained from transplanted tumor systems which entail artefactual immunity associated with viral or chemical induction of the tumors or their allogeneic transplantation." *See* Hewitt *et al.*, abstract, page 241. Thus, a person of skill in the art would not have had a reasonable expectation of success, based on the Fugiwara results, that an effective

human vaccine having the properties described and claimed herein could be produced by conjugating hapten to human tumor cells.

The Fujiwara 1984 reference adds no further expectation of success. It describes a local administration (injection directly into the tumor) of a hapten TNP (not TNP-conjugated tumor cells) in two transplantable tumor systems. (*See* page 510, 2nd col., 1st ¶, and page 511, 2nd col., 1st ¶) The present vaccine composition is effective when administered systemically and has the property of eliciting T lymphocytes that infiltrate the tumor of the treated human and are capable of inducing inflammation in the tumor. Based on the teaching of Fujiwara 1984, a person of skill in the art could not have reasonably expected that systemic administration of human tumor cells conjugated to a hapten would elicit T lymphcytes or cause tumor inflammation in humans. In fact, this would have been entirely unpredictable based on Fujiwara 1984 alone or in combination with the above cited references.

The Getzy reference cannot overcome the deficiency of the McCune, Berd and Fugiwara references. The Getzy reference teaches that dinitrochlorobenzene (DNCB) and 1-fluoro-2,4-dinitrochlorobenzene may be interchangeable. The reference is silent as to any therapeutic treatment of cancer.

The Examiner acknowledges that the properties of the present invention (*e.g.* inflamatory immune response or infiltration of tumor by activated T cells) are not taught by the cited references. However, she states that these properties are inherent properties of the combined cited references, and that the claimed method is anticipated because of these inherent properties. Applicant respectfully disagrees.

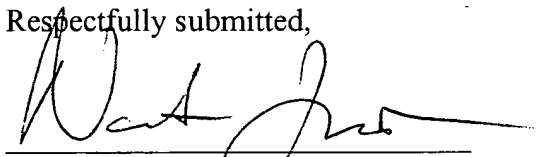
The claimed composition and method cannot be anticipated by a combination of prior art references. It is well established that, to anticipate, a single prior art reference must disclose (literally or inherently) all limitations of the claim. This is not the case here: none of the cited references discloses a hapten-conjugated human tumor cell or its use in a method of treatment. Accordingly, Ex parte Novitski, 26 USPQ 7389 (Bd. Pat. App. & Inter. 1993), which pertains to inherent anticipation (by a single reference), is not applicable.

In view of the remarks set forth above, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 43, 44 and 47 under 35 U.S.C. §103.

CONCLUSION

In view of the amendments to the pending claims and the above remarks, reconsideration of this application is respectfully requested and a favorable determination is solicited.

Respectfully submitted,



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Br. J. Cancer (1976) 33, 241

A CRITIQUE OF THE EVIDENCE FOR ACTIVE HOST DEFENCE AGAINST CANCER, BASED ON PERSONAL STUDIES OF 27 MURINE TUMOURS OF SPONTANEOUS ORIGIN

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Summary.—Extensive experience with isotransplants of 27 different tumours (leukaemias, sarcomata, carcinomata), all of strictly spontaneous origin in laboratory bred mice of low cancer strains CBA/Ht and WHT/Ht, has revealed no evidence of tumour immunogenicity. Of approximately 20,000 maintenance transplants, none failed and none regressed; of almost 10,000 carefully observed tumours arising from small or minimal inocula of tumour cells, none spontaneously regressed. The number of injected viable tumour cells required to give a 50% probability of successful transplantation (the TD_{50}) ranged from ~ 1 cell to $> 10{,}000$ cells among the 27 tumours; high TD_{50} values, which were dramatically reduced by various procedures having no immunological significance, did not signify active " resistance " of the hosts. In the case of all of 7 randomly selected tumours, prior " immunization " of recipients with homologous lethally irradiated cells *increased* their tumour receptivity.

Several experiments using various tumours failed to give evidence that immunity could be non-specifically induced or that a massive preponderance of lymphocytes from specifically sensitized mice could inhibit tumour transplantation or growth *in vivo*; no trace of " resistance " to tumour was adopted by isogeneic recipients of lymphocytes from regional nodes of tumour bearers. A limited review of the recent literature on tumour immunity shows that practically all the animal data presented in support of a general theory of tumour immunogenicity or to provide a basis for active clinical immunotherapy have been obtained from transplanted tumour systems which entail artefactual immunity associated with viral or chemical induction of the tumours or their allogeneic transplantation. It is suggested that isotransplants of spontaneously arising tumours are the only appropriate models of human cancer and that any genuine rapport between the animal laboratory and the clinic requires their exclusive use.

WE REPORT here a considerable volume of data concerning the transplantation characteristics of a large number and variety of murine tumours having the distinction that they were all of strictly spontaneous origin in low cancer strain mice. The data, collected over many years of experimentation, have some additional claim to uniqueness from the exceptionally uniform conditions under which the information was obtained: the breeding colonies of inbred mice have been managed in every detail by one of us (A.S.W.); all other technical procedures have been carried out personally by the authors without additional assistance; to validate comparison of data between different tumours and from time to time over long periods of any one tumour's history, the routine technical procedures have not been varied in any significant particular; and, finally, a detailed record has been kept of the fate of every mouse used in every experiment, permitting the retrospective analysis of our experience which we are to report.